Remarks

The present application is a 371 Application of PCT/GB00/02361. Applicants wish to correct a clerical error that occurred in the preparation of the National Transmittal Letter. The Transmittal Letter states that the application was filed in the United States Receiving Office but the application was actually filed in the Great Britain Receiving Office. Furthermore, when the application entered National Phase, the IPER and an Annex of substitute pages were included as acknowledged in the Notice of Acceptance. These pages included amendments to the specification and replacement claims. The Examiner, however, examined the claim set originally filed in the PCT Application. For the sake of clarity, Applicants have amended the claim set already examined by the Examiner.

The specification has been amended to include reference to WO 93/04682 and corresponds with the amendment to the specification made during the International Phase of the PCT application. Entry of this amendment is respectfully requested.

Claim 1 has been amended to address issues raised by the Examiner and to conform with amendments introduced during the International Phase of the PCT application. Claim 9 has been cancelled. Claim 10 has been amended to address issues raised by the Examiner. New Claim 11 has been added to more specifically claim aspects of the present invention. Applicants assert that these amendments raise no issue of new matter. Basis for the amendment to Claim 10 may be found at page 12, lines 1-5 of the specification. Basis for new Claim 11 may be found at page 12, lines 7-16 of the specification. Applicants respectfully request entry of these amendments.

Rejections Under 35 U.S.C. §§ 101 and 112, second paragraph

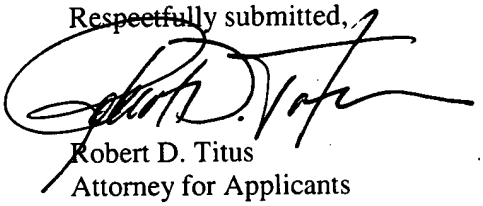
The Examiner rejected Claim 9 under 35 U.S.C. §§ 101 and 112, second paragraph. Claim 9 has been cancelled, thereby obviating the Examiner's rejection. Withdrawal of these rejections in view of the cancellation of the claim is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claims 1, 2, 3, 7, 8, and 10 stand rejected under 35 U.S.C. § 102(b) as anticipated by Jones (WO 93/13079) and Reitz (WO 93/04682). Claim 1 has been amended to exclude those compounds disclosed in Jones and Reitz. As such, Claim 1 and dependent Claims 2, 3, 7, and 8 no longer encompass the subject matter raised by the Examiner. Claim 10 has been amended to exclude the treatment of anxiety and aggression disclosed in Reitz.

Entry of the amendments, and withdrawal of the rejection in view of the amendments are respectfully requested.

Respectfully submitted,



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17 March 2004

UNITED STATES PATENT AND TRADEMARK OFFICE

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US APPLICATION NUMBER NO	FIRST NAMED APPLICANT	ATTY DOCKET NO
10/031,122	Sandra Ginette Milutinovi	G-1344

INTERNATIONAL APPLICATION NO	
PCT/GB00/02361	
IA FILING DATE	PRIORITY DATE
06/15/2000	07/13/1999

Janet A Gongola
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Lilly Corporate Center DC1104
Indianapolis, IN 46285

CONFIRMATION NO. 6297
371 ACCEPTANCE LETTER

OC000000007944913

Date Mailed: 04/24/2002

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an Electèd Office (37 CFR 1.495) , has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

01/09/2002	01/09/2002
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- U.S. Basic National Fee
- Assignee Statement
- Copy of IPE Report
- Copy of the International Application
- Copy of the International Search Report
- Oath or Declaration

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

FRANCINE YOUNG
Telephone: (703) 305-3662

PART 1 - ATTORNEY/APPLICANT COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
G.1344 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02361	15/06/2000	13/07/1999
International Patent Classification (IPC) or national classification and IPC C07C311/37		
Applicant ELI LILLY AND COMPANY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/02/2001	17.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tél. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mercey, J Telephone No. +49 89 2399 8956

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02361

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

2-30	as originally filed			
1	as received on	30/07/2001	with letter of	27/07/2001

Claims, No.:

1-15	as received on	30/07/2001	with letter of	27/07/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 7, with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7,11-13
	No:	Claims	8-10,14,15
Inventive step (IS)	Yes:	Claims	1-7,11-13

	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,8-15
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 27/7/01 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the first, fourth and fifth compounds of the disclaimer in Claim 8, it appearing that said compounds do not belong to the state of the art, disclaimers only being allowed in order to overcome an accidental novelty destroying disclosure.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 : DE-C-726386
D2 : WO-A-9313079
D3 : J. Med. Chem., 1992, 35(5), 847-58
D4 : WO-A-9304682

NOVELTY

The present application does not meet the requirements of Article 33(2) PCT because the subject-matter of Claims 8-10, 14 and 15 is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT), the disclaimer in Claim 8 excluding compounds 51 and 57 of D2, but **not** those of D1 and D3.

Thus D1 discloses a compound according to present Claims 8-10, namely the product of Ex. 13, which is a compound of present formula (I) wherein R^1 is H, R^2 is methyl, R^3 and R^4 are **ethyl**, and the sulfonamide is at the 4-position. Said compound is described as being active against bacterial infections (cf. page 1, lines 26-36), and is thus also novelty destroying for present Claims 14 and 15.

D3 discloses two compounds according to present Claims 8 and 9, namely compounds 29h and 30h in Scheme III on page 851 (the preparations of which are described on pages 855 and 856), which are compounds of present formula (I) wherein R^1 and R^2, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 5 carbon atoms fused to a substituted phenyl group, R^3 and R^4, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 carbon atoms and a further nitrogen atom i.e. a piperazinyl group, and the sulfonamide is at the 4-position.

INVENTIVE STEP (Article 33(3) PCT)

In the light of D4, which teaches 4-arylpiperazines and 4-arylpiperidines as antipsychotic agents, the problem to be solved by the present invention may be regarded as the provision of compounds which modulate the activity of neuronal calcium channels for use in the treatment of CNS disorders.

The solution provided by the compounds of Claim 1 are the benzenesulphonamides of formula (I) substituted at the 3- or 4-position by an aminomethyl group. Said compounds differ from those of D4 in view of the fact that when R^1 and R^2, together with the nitrogen atom to which they are attached, form a carbocyclic group, this may be substituted by 1-3 methyl or ethyl groups only, whereas in D4, the corresponding heterocycle is always substituted by the group Ar. There is no suggestion, either in D4 or in any other cited art, that by modifying the D4 compounds in this way, compounds with neuronal calcium channel modulating activity may be obtained, such an activity not being disclosed in D4, nor in any of the other cited art. D1-D3 are irrelevant to the question of inventive step, the compounds of D2 and D3 falling under the present formula (I) of Claim 1 being disclosed therein as intermediates only, and the compound of D1 for use in bacterial infections. Hence the use of the compounds of formula (I) according to Claims 1-6, the method of Claim 7, and the novel compounds of Claims 11-13 are inventive.

INDUSTRIAL APPLICABILITY

For the assessment of the present Claim 7 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of

claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

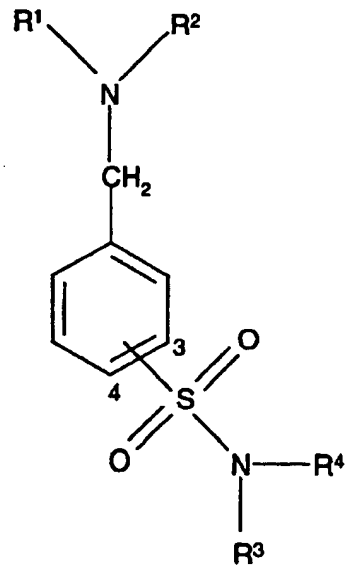
SULFONAMIDE SUBSTITUTED BENZYLAMINE DERIVATIVES AND THEIR USE AS MEDICAMENTS

This invention relates to novel chemical compounds and their use as pharmaceuticals.

It is well known that chemical compounds which modulate the activity of neuronal calcium channels are potentially useful in treating disorders of the central nervous system.

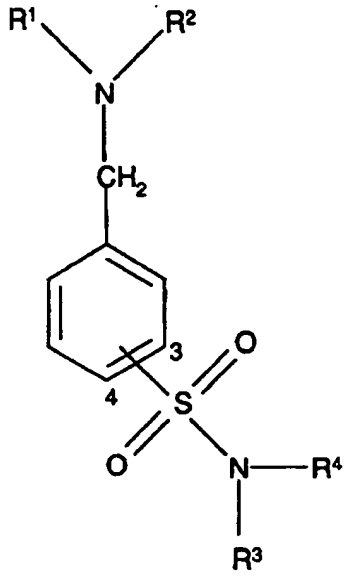
WO 93/04682 describes 4-arylpiperazines and 4-arylpiperidines useful for the treatment of disorders such as anxiety and aggression.

The compounds of the invention have the following general formula:



(I)

1. Use of a compound of the formula



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms

optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group; or a salt thereof; for the manufacture of a medicament for treating a disorder of the central nervous system.

2. Use according to Claim 1 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4 together with the nitrogen atom to which they are attached, form a carbocyclic group.

3. Use according to Claim 2 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen.

4. Use according to Claim 3 in which R^1 is hydrogen, R^2 is optionally substituted phenyl-C_{1-4} alkyl and R^3 and R^4 are C_{1-6} alkyl.

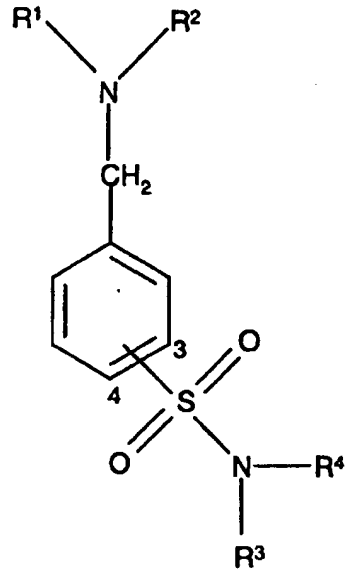
5. Use according to Claim 1 in which R^2 is $-(CH_2)_2NR^5R^6$.

6. Use according to Claim 1 or 5 in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

7. A method of treating a disorder of the central nervous system which comprises administering an effective

amount of a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

8. A compound of the formula



(I)

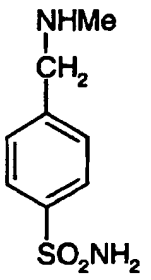
in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group; or a salt thereof; with the proviso that said compound of formula (I) is not a compound of formulae:



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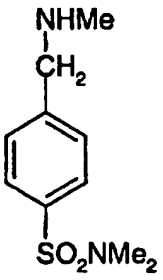

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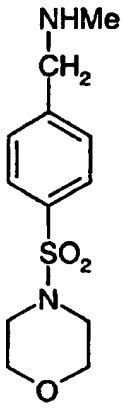

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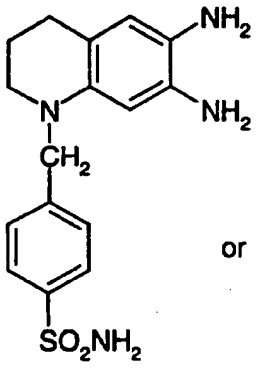
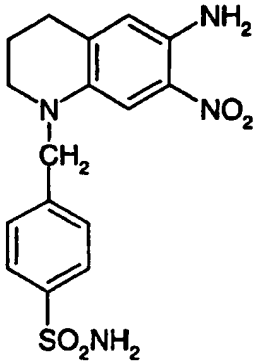


or


9. A compound according to Claim 1 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1

and R^2, or R^3 and R^4 together with the nitrogen atom to which they are attached, form a carbocyclic group.

10. A compound according to Claim 9 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen.

11. A compound according to Claim 10 in which R^1 is hydrogen, R^2 is optionally substituted phenyl-C_{1-4} alkyl and R^3 and R^4 are C_{1-6} alkyl.

12. A compound according to Claim 8 in which R^2 is $-(CH_2)_2NR^5R^6$.

13. A compound according to Claim 8 or 12 in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

14. A pharmaceutical formulation comprising a compound according to any of Claims 8 to 13 or a pharmaceutically acceptable salt thereof, together with a diluent or carrier therefor.

15. A compound according to any of Claims 8 to 13, for use as a pharmaceutical.

PATENT Dkt No. G-1344 Atty JAG

RECEIVED BY THE UNITED STATES PATENT & TRADEMARK OFFICE:

Org ___, CIP ___, Div ___, Con ___, Prov ___, PCT Nat'l ✓, CPA ___
Application of: Sandra Ginette Milutinovic, et al.
Titled: Sulfonamide Substituted Benzylamine Derivatives and their use as Medicaments
Consisting of Fee Transmittal, Utility Patent Transmittal and:
Claims, Abstract, Specification (___ pages), Drawings (___ sheets)
Declaration and Power of Attorney ___ National Phase Declaration ✓
Preliminary Amendment ___ Stmt 821 ___; Diskette ___
Recordation/Assignment ✓ IDS/1449 ___
Miscellaneous Papers:

IPER 10/031122
JC07 Rec'd PCT/PTO 09 JAN 2002

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